

PYRAZOLE DERIVATIVES AS GNRH INHIBITORS

10/525111

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a
5 medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-
10 stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes,
15 including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

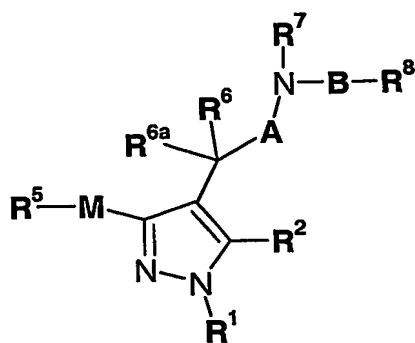
It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions
20 such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists:

WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO
25 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

30 It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),

- 2 -

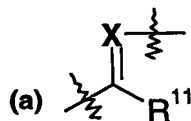


Formula (I)

wherein

A represents a direct bond or optionally substituted C₁₋₅alkylene;

5 B is a group of Formula (II):



Formula (II);

wherein at position (a) Formula (II) is attached to the nitrogen atom and the group X is attached to R⁸;

10 M is -(CH₂)₀₋₂-O-;

R¹ represents hydrogen; optionally substituted C₁₋₈alkyl; or (CH₂)_b-R^a, wherein

R^a represents C₃₋₈cycloalkyl and b is zero or an integer from 1 to 6;

R² represents an optionally substituted mono- or bi-cyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR³R^{3a}, optionally substituted

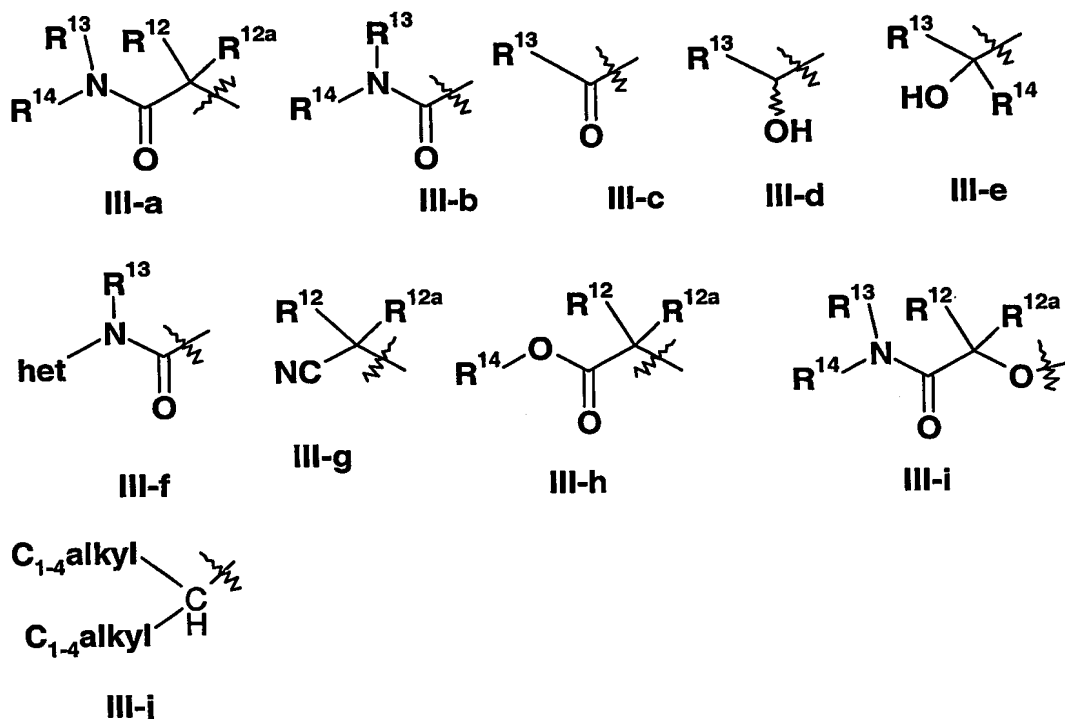
15 C₁₋₈alkyl, optionally substituted C₁₋₈alkoxy or halo;

R³ and R^{3a} are independently selected from hydrogen; optionally substituted C₁₋₈alkyl and optionally substituted aryl;

R⁵ is selected from an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; or a group of formula

20 III-a; III-b; III-c; III-d; III-e; III-f, III-g, III-h, III-i or: III-j;

- 3 -




wherein **het** represents an optionally substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

R^6 and R^{6a} , are independently selected from hydrogen and optionally substituted C_{1-8} alkyl;

5 or R^6 and R^{6a} together represent carbonyl;

R^7 represents hydrogen or optionally substituted C_{1-8} alkyl;

or R^6  $A-N-R^7$ together from an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms independently selected from O, N and S, and R^{6a} represents hydrogen and optionally substituted C_{1-8} alkyl;

10 **X** and R^8 are selected from:

(i) **X** represents N and R^8 is selected from:

cyano, hydrogen, hydroxy, $-O-R^b$, $-NR^bR^c-C(O)O-R^b$, $-CONR^bR^c$ or $NH-C(O)-R^b$, where R^b and R^c are independently selected from hydrogen and C_{1-4} alkyl optionally substituted with hydroxy, amino, N- C_{1-4} alkylamino, N,N-di- C_{1-4} alkylamino, HO- C_{2-4} alkyl-NH- or HO- C_{2-4} alkyl-N(C_{1-4} alkyl)-;

15

(ii) **X** represents CH and R^8 represents NO_2 ; and

(iii) **X-R**⁸ represents O;

R^{11} is a group of the formula: $N(R^9R^{10})$ wherein R^9 represents hydrogen, aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally-substituted

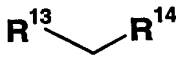
- 4 -

C_{1-8} alkyl and R^{10} represents hydrogen or optionally substituted C_{1-8} alkyl; or the structure $N(R^9R^{10})$ represents an optionally-substituted 3- to 10 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;

- 5 R^{12} and R^{12a} are independently selected from hydrogen or optionally substituted C_{1-8} alkyl; or R^{12} and R^{12a} together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

R^{13} and R^{14} are selected from:

- 10 (i) R^{13} is selected from hydrogen; optionally substituted C_{1-8} alkyl; optionally substituted aryl; $-R^d-Ar$, where R^d represents C_{1-8} alkylene and Ar represents optionally substituted aryl; and optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and R^{14} is selected from hydrogen; optionally substituted C_{1-8} alkyl and optionally substituted aryl;
- 15 (ii) where R^5 represents a group of formula III-a, III-b or III-i, then the group $NR^{13}(-R^{14})$ represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

- 20 (iii) where R^5 represents structure III-e, then the group  represents an optionally substituted 3 to 8 membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I), or salt, pro-drug or
25 solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I), or salt, pro-drug or solvate thereof:

- (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- 30 (b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and
- (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient,

- 5 -

preferably a sex hormone related condition selected from prostate cancer and pre-menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a
5 compound of Formula (I), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

10 Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl**, **alkylene** or **alkenyl** moiety may be linear or branched.

15 The term "**alkylene**" refers to the group $-\text{CH}_2-$. Thus, C_8 alkylene for example is $-(\text{CH}_2)_8-$.

The term "**aryl**" refers to phenyl or naphthyl.

The term "**carbamoyl**" refers to the group $-\text{CONH}_2$.

The term "**halo**" refers to fluoro, chloro, bromo or iodo.

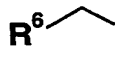
20 The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring or a 5-10 membered saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to
25 the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is an aromatic bicyclic ring system comprising a 6-membered ring fused to
30 either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinoliny, isoquinoliny, quinoxaliny, quinazoliny, phthalaziny,

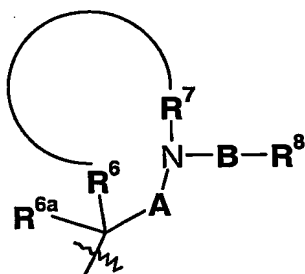
- 6 -

cinnoliny and naphthyridiny. Examples of saturated or partially saturated heterocyclic rings include pyrroliny, pyrrolidinyl, morpholiny, piperidinyl, piperazinyl, dihydropyridiny and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O₂) group.

- 5 The term "aromatic ring" refers to a 5-10 membered aromatic mono or bicyclic ring optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4
10 thienyl and pyridyl.

The symbol  denotes where the respective group is linked to the remainder of the molecule.

- For the avoidance of doubt, when R^6  $A-N-R^7$ together form an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 3 further heteroatoms
15 independently selected from O, N and S, then the groups shown cyclise to form a nitrogen-containing heterocyclic ring, i.e



, optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S.

- Examples of **C₁₋₈alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl,
20 *tert*-butyl and 2-methyl-pentyl; example of **C₁₋₈alkylene** include: methylene, ethylene and 2-methyl-propylene; examples of **C₁₋₈alkoxy** include methoxy, ethoxy and butyloxy; examples of **N-C₁₋₄alkylamino** include N-methylamino and N-ethylamino; examples of **N,N-di-C₁₋₄alkylamino**, examples of **HO-C₂₋₄alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropylamino, examples of **HO-C₂₋₄alkyl-N(C₁₋₄alkyl)** include
25 N-methyl-hydroxymethylamino, N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropylamino.

It is to be understood that, insofar as certain of the compounds of the invention may

- 7 -

exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

Preferred compounds of Formula (I) are those wherein any one of the following or a combination of the following apply.

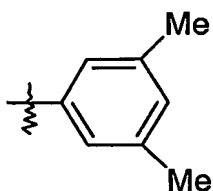
Preferably A represents optionally substituted C₁₋₅alkylene. Further preferably C₁₋₄alkylene. Most preferably methylene or ethylene.

Preferably M is -CH₂-O-.

Preferably R¹ represents hydrogen or optionally substituted C₁₋₆alkyl. More preferably R¹ represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably R¹ represents hydrogen.

Preferably R² represents an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano, NR^eR^f, optionally substituted C₁₋₈alkyl (preferably, C₁₋₄alkyl, eg, methyl or ethyl), optionally substituted C₁₋₈alkoxy (preferably, C₁₋₆alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein R^e and R^f are independently selected from hydrogen, C₁₋₆alkyl or aryl. Further preferably R² is optionally substituted phenyl wherein the optional substituents are selected from cyano, NR^eR^f, optionally substituted C₁₋₄alkyl, optionally substituted C₁₋₆alkoxy, F, Br or Cl wherein R^e and R^f are as defined above. Yet further preferably R² is optionally substituted phenyl wherein the optional substituents are selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably R² represents

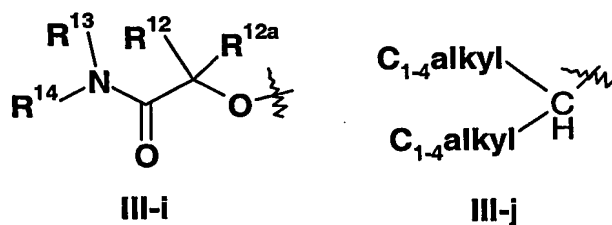
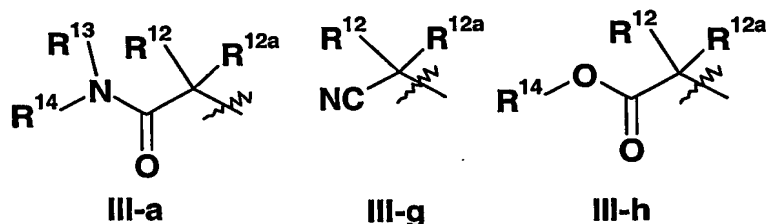
- 8 -



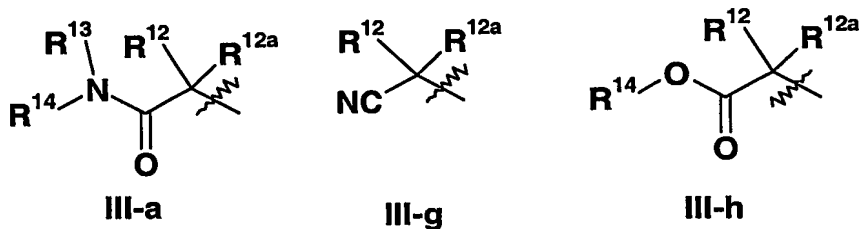
wherein Me represents methyl. Preferably R^2 bears 1, 2 or 3 substituents.

Preferably R^3 and R^{3a} are independently selected from hydrogen; optionally substituted C_{1-6} alkyl and , optionally substituted aryl . Further preferably R^3 and R^{3a} are independently
5 selected from methyl, ethyl, *tert*-butyl and phenyl.

Preferably R^5 is selected from a group of formula III-a , III-g, III-h, or III-i or: III-j

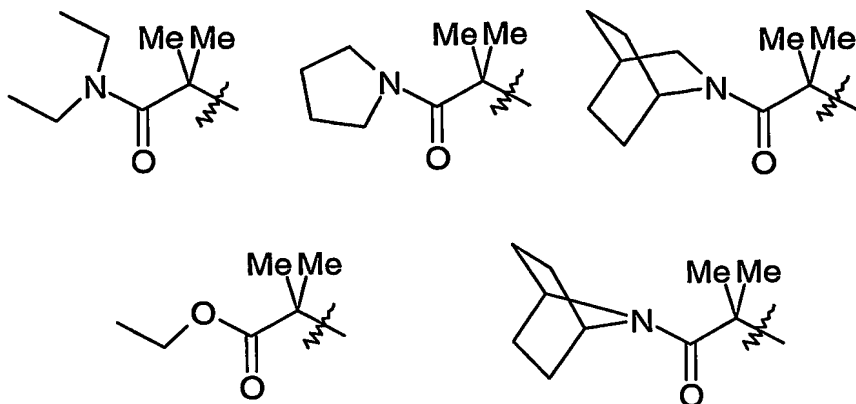


Further preferably R^5 is selected from one of the following groups:



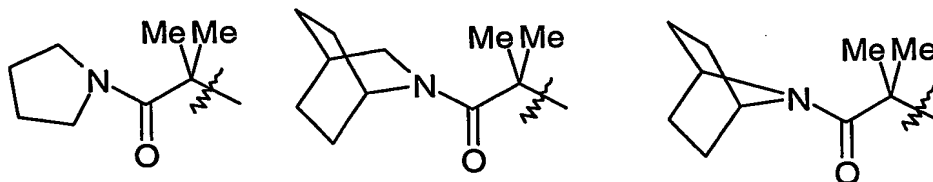
- 9 -

Yet further preferably R^5 is selected from one of the following groups:



wherein Me represents methyl.

Most preferably R^5 is selected from one of the following groups:



5

In one embodiment, R^6 and R^{6a} each represent hydrogen and A represents C_{1-4} alkylene (preferably methylene).

In a further embodiment of the invention R^6 represents hydrogen, R^{6a} represents methyl,
10 and A represents C_{1-4} alkylene (preferably methylene).

Preferably R^7 is selected from hydrogen or optionally-substituted C_{1-6} alkyl. Further preferably R^7 represents hydrogen, methyl, ethyl or *tert*-butyl.

Preferably X and R^8 represent either:-

- 15 (a) X represents N and R^8 represents cyano or $-C(O)O-R^b$; or
(b) X represents N and R^8 represents hydrogen.

Further preferably X represents N and R^8 represents cyano or $-C(O)O-R^b$; wherein R^b represents C_{1-6} alkyl;

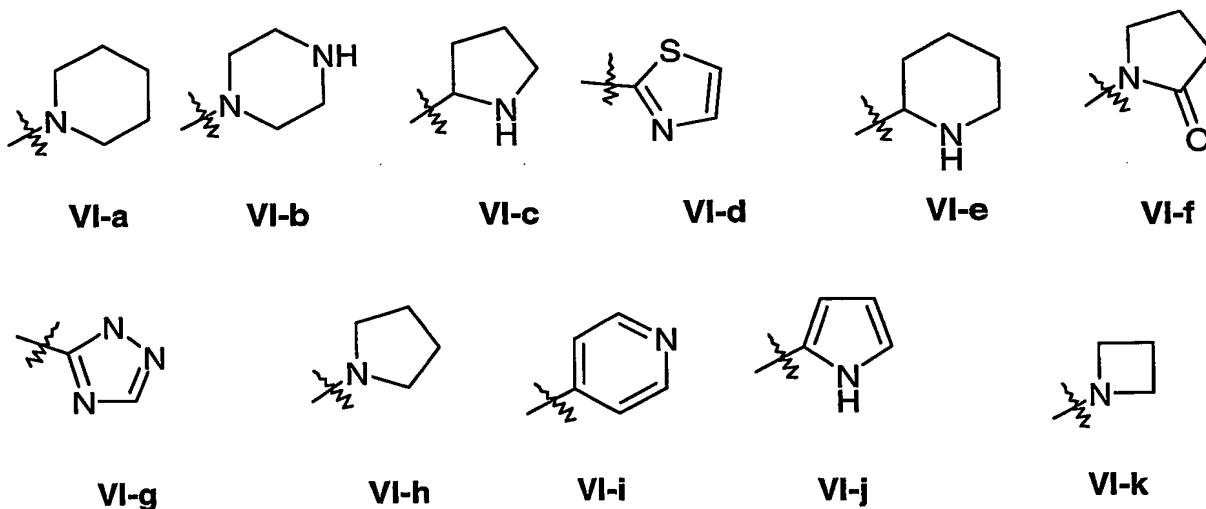
In a further embodiment of the invention X represents N and R^8 represents $-CONR^bR^c$
20 wherein R^b and R^c are as defined above.

Preferably R^9 comprise part of the group $N(R^9R^{10})$ or is hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted C_{1-4} alkyl wherein the optional substituents are selected from: hydroxy, amino,

- 10 -

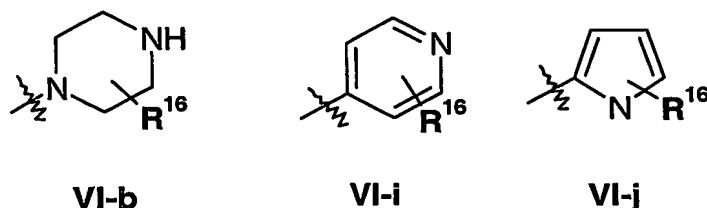
nitro, cyano, optionally-substituted aryl, optionally substituted 3- to 8- membered heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, $-O-R^b$, $C(O)NR^bR^c$, $-NR^bR^c$, $-NR^cC(O)-R^b$, $-C(O)NR^bR^c$, $-NR^cS(O_{0-2})R^b$, $-S(O_{0-2})R^b$, wherein R^b and R^c are as defined above.

- 5 When R^9 is a C_{1-6} alkyl group substituted by an optionally-substituted 3 to 10 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S, the heterocyclic ring is preferably selected from pyridyl, thienyl, piperidinyl, imidazolyl, triazolyl, thiazolyl, pyrrolidinyl, piperazinyl, morpholinyl, imidazolinyl, benzotriazolyl, benzimidazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl, furanyl, pyrrolyl,
- 10 1,3-dioxolanyl, 2-azetynyl, each of which is optionally substituted. Further preferably a group of formula VI-a, VI-b, VI-c, VI-d, VI-e, VI-f, VI-g, VI-h, VI-i, VI-j or VI-k:, wherein each group is optionally substituted by one or more groups selected from R^{16} .



15 .

Most preferably a group of formula VI-b, VI-i or VI-j:



wherein

- R^{16} represents hydrogen, aryl, a 3- to 10 membered heterocyclic ring or optionally substituted
- 20 C_{1-4} alkyl wherein the optional substituents are selected from: hydroxy, amino, nitro, cyano, optionally-substituted phenyl, optionally substituted 3- to 8- membered heterocyclyl

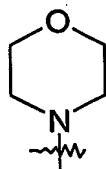
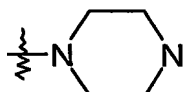
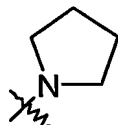
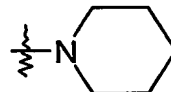
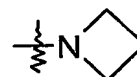
- 11 -

containing from 1 to 4 heteroatoms independently selected from O, N and S, $-O-R^b$, $C(O)NR^bR^c$, $-NR^bR^c$, $-NR^cC(O)-R^b$, $-C(O)NR^bR^c$, $-NR^cS(O_{0.2})R^b$, $-S(O_{0.2})R^b$, wherein R^b and R^c are as defined above;

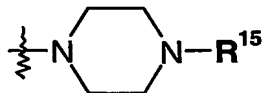
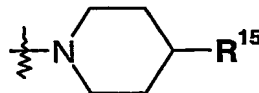
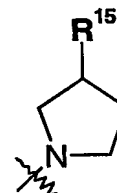
- Preferably R^{10} comprises part of the group $N(R^9R^{10})$ or is optionally substituted C_{1-6} alkyl. Further preferably R^{10} comprises part of the group $N(R^9R^{10})$ or is selected from: methyl, ethyl or *tert*-butyl.

When $N(R^9R^{10})$ represent an optionally substituted 3- to 10- membered heterocyclic ring, $N(R^9R^{10})$ is preferably selected from a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S.

- 10 Further preferably a 5- or 6-membered monocyclic ring containing between 1 and 3 (preferably 1 or 2) heteroatoms independently selected from O, N and S, selected from pyrrolidinyl, thienyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl piperazinyl, imidazole, azetidiny or azetiny. Further preferably the structure $N(R^9R^{10})$ is a heterocyclic ring selected from an optionally-substituted group of formula, **IV-a**, **IV-b**, **IV-c**, **IV-d** and **IV-e**, wherein the optional substituents are preferably selected from the groups listed for R^{15}
- 15 below

**IV-a****IV-b****IV-c****IV-d****IV-e**

Further preferably the structure $N(R^9R^{10})$ is selected from a group of formula **Va**, **Vb** or **Vc**:

**V-a****V-b****V-c**

- 20 Most preferably the structure $N(R^9R^{10})$ is a group of formula **V-c**:

R^{15} represents hydrogen, optionally substituted aryl, an optionally substituted 3- to 10 membered heterocyclic ring or optionally substituted C_{1-4} alkyl wherein the optional substituents on aryl, a heterocyclic ring or C_{1-4} alkyl are selected from: hydroxy, amino, nitro, cyano, halo, optionally-substituted aryl, optionally substituted 3- to 8- membered

- 12 -

heterocyclyl containing from 1 to 4 heteroatoms independently selected from O, N and S, -O-R^b, C(O)NR^bR^c, -NR^bR^c, -NR^cC(O)-R^b, -C(O)NR^bR^c, -NR^cS(O₀₋₂)R^b, -S(O₀₋₂)R^b, wherein R^b and R^c are as defined above. Preferably R¹⁵ is heterocyclyl. Further preferably R¹⁵ is selected from: pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl or thiazolyl. Most

5 preferably R¹⁵ is pyridyl.

In a further embodiment of the invention N(R⁹R¹⁰) represent an optionally substituted 3- to 10- membered heterocyclic ring, wherein the optional substituents are selected from R¹⁵ as defined above.

Preferably R¹² and R^{12a} are independently selected from: hydrogen, optionally
10 substituted C₁₋₆alkyl or R¹² and R^{12a} together with carbon to which they are attached from an optionally substituted 3- to 6-membered cycloalkyl ring. Further preferably R¹² and R^{12a} are independently selected from: hydrogen, methyl, ethyl or *tert*-butyl. Most preferably R¹² and R^{12a} are both methyl.

Preferably R¹³ and R¹⁴, are independently selected from hydrogen, optionally
15 substituted C₁₋₆alkyl, optionally substituted phenyl and -R^d-phenyl, where R^d represents C₁₋₆alkylene or and an optionally substituted 3- to 8- membered heterocyclic ring (preferably, a 5- or 6-membered monocyclic ring) containing from 1 to 3 (preferably 1 or 2) further heteroatoms independently selected from O, N and S. Further preferably R¹³ and R¹⁴, are independently selected from hydrogen or C₁₋₆alkyl.

20 Where optional substitution is mentioned at various places, this refers to one, two, three or more optional substituents. Unless otherwise indicated above (ie, where a list of optional substituents is provided), each substituent can be independently selected from C₁₋₈alkyl (eg, C₂₋₆alkyl, and most preferably methyl, ethyl or *tert*-butyl); C₃₋₈cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxo; C₁₋₆alkoxy, preferably methoxy or C₂₋₄alkoxy;
25 halo, preferably Cl or F; Hal₃C-, Hal₂CH-, HalCH₂-, Hal₃CO-, Hal₂CHO or Hal CH₂O, wherein Hal represents halo (preferably F); R^gCH₂O-, R^hC(O)N(R)-, R^hSO₂N(R)- or R^g-R^hN-, wherein R^g and R^h independently represent hydrogen or C₁₋₈alkyl (preferably methyl or C₂₋₆alkyl or C₂₋₄alkyl), or R^g-R^hN- represents an optionally substituted C₃₋₈, preferably C₃₋₆, heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected
30 from O, N and S; hydrogen; or R^kC(O)O- or R^kC(O)-, R^k representing hydrogen, optionally substituted phenyl or C₁₋₆alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by R^g-R^hN-, at least one (eg, one, two or three) substituents may be provided independently selected from C₁₋₆alkyl (eg,

- 13 -

c₂₋₄alkyl, more preferably methyl); phenyl; CF₃O-; F₂CHO-; C₁₋₈alkoxy, preferably methoxy, ethoxy or C₃₋₆alkoxy; C₁₋₈alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C₃₋₆alkoxyC(O)-; phenoxycarbonyl; phenoxy; C₁₋₈alkanoyl, preferably acetyl, ethanoyl or C₃₋₆alkanooyl; carboxy; C₁₋₈alkylS(O)_{nn} wherein **nn** is an integer between 0 and 2, preferably methylthio, ethylthio, C₃₋₆alkylthio, methylsulphinyl, ethylsulphinyl, C₃₋₆alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C₃₋₆alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); **R^mRⁿN-** where **R^m** and **Rⁿ** are independently hydrogen or C₁₋₆alkyl (preferably C₂₋₄alkyl, more preferably methyl, most preferably **R^m=Rⁿ=methyl**); and nitro.

- 10 Where optional substitution of a ring is mentioned at various places, this most preferably refers to one, two, three or more substituents selected from C₁₋₈alkyl (eg, C₂₋₆alkyl, and most preferably methyl); C₁₋₈alkoxy, preferably methoxy, ethoxy or C₃₋₆alkoxy; C₁₋₈alkylS(O)_{nn} wherein **nn** is an integer between 0 and 2, preferably methylthio, ethylthio, C₃₋₆alkylthio, methylsulphinyl, ethylsulphinyl, C₃₋₆alkylsulphinyl, methylsulphonyl, ethylsulphonyl or C₃₋₆alkylsulphonyl; halo (eg, F, Cl or Br); cyano; and NO₂.

A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

R¹¹ is a group of the formula: N(**R⁹R¹⁰**); and

- 20 **N(R⁹R¹⁰)** represents an optionally-substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S, preferably substituted by heterocyclyl;

or a salt, pro-drug or solvate thereof.

A preferred group of compounds of the invention comprise compounds of Formula (I) wherein:

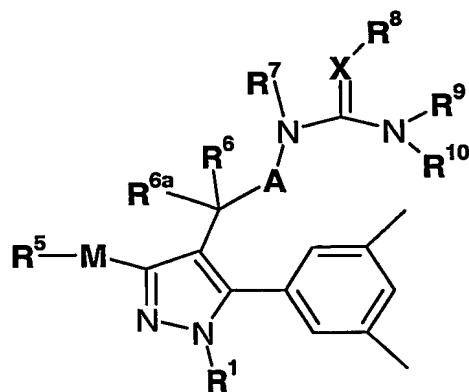
- 25 **R¹¹** is a group of the formula: N(**R⁹R¹⁰**);

R⁹ is a C₁₋₆alkyl group substituted by an optionally-substituted 3 to 8 membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S; and

- R¹⁰** represents hydrogen or C₁₋₆alkyl
30 or a salt, pro-drug or solvate thereof.

- 14 -

A preferred group of compounds of the invention comprises a compound of Formula (Ia):

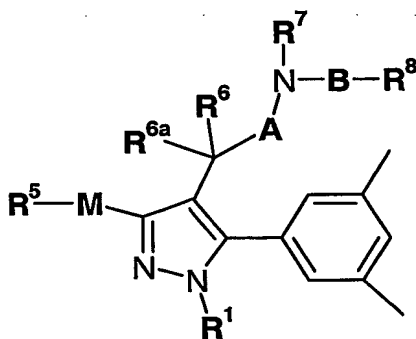


Formula (Ia)

5 wherein:

A, B, M, X, R¹, R⁵, R⁶, R^{6a}, R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹² and R^{12a} are as defined above;
or a salt, pro-drug or solvate thereof.

A preferred group of compounds of the invention comprises a compound of Formula (Ib):



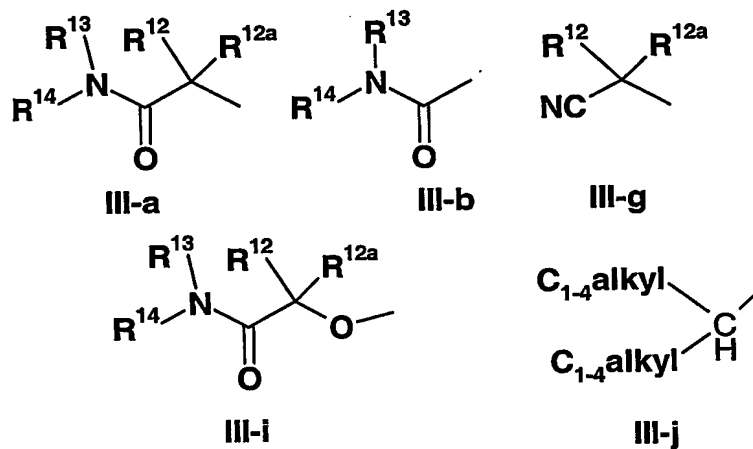
Formula (Ib)

10

wherein:

- 15 -

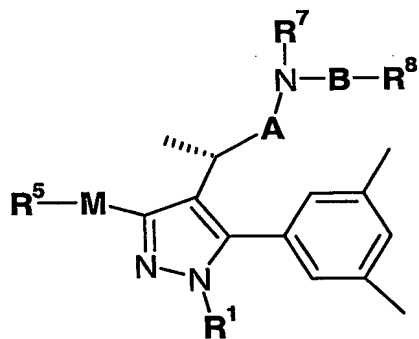
R^5 is selected from: IIIa, IIIb, IIIg, IIIi or IIIj:



and A, B, M, X, R^1 , R^5 , R^6 , R^{6a} , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{12a} , R^{13} , and R^{14} are as defined above;

5 or a salt, pro-drug or solvate thereof.

A further preferred group of compounds of the invention comprises a compound of Formula (Ic):

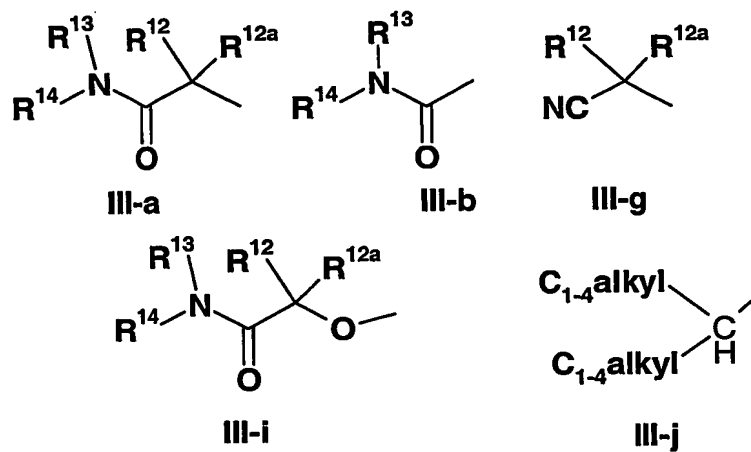


Formula (Ic)

10 wherein:

- 16 -

R^5 is selected from a **IIIa**, **IIIb**, **IIIg**, **IIIi** or **IIIj**:

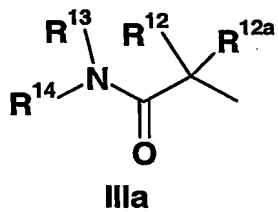


and A, B, M, X, R^1 , R^6 , R^{6a} , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{12a} , R^{13} , and R^{14} are as defined above;

5 or a salt, pro-drug or solvate thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (Ia), (Ib) or (Ic) wherein:

R^5 is a group of formula **IIIa**:



10 $NR^{13}(-R^{14})$ represents an optionally substituted 7- to 8- membered bicyclic heterocyclic ring and A, B, X, R^1 , M, R^6 , R^{6a} , R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} and R^{12a} are as defined above; or a salt, pro-drug or solvate thereof.

A preferred compound according to the present invention is:

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-
 15 4-[1S-methyl-2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrazole;
 or a salt, pro-drug or solvate thereof.

- 17 -

In a further embodiment particularly preferred compounds according to the present invention are wherein the compound is selected from:

- isopropyl (1Z)-({2-[3-(2,2-dimethyl-3-oxo-3-pyrrolidin-1-ylpropoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;
- 5 isopropyl (1Z)-({2-[3-(2,2-dimethyl-3-oxo-3-(7-azabicyclo[2.2.1]hept-7-yl)propoxy)-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;
- 10 isopropyl (1Z)-({2-[3-[3-(diethylamino)-2,2-dimethyl-3-oxopropoxy]-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}amino)(3-pyridin-4-ylpyrrolidin-1-yl)methylidenecarbamate;
- N*-{2-[3-[3-(diethylamino)-2,2-dimethyl-3-oxopropoxy]-5-(3,5-dimethylphenyl)-1*H*-pyrazol-4-yl]ethyl}-3-pyridin-4-ylpyrrolidine-1-carboxamide;
- or a salt, pro-drug or solvate thereof.

- 15 According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (Ia), Formula (Ib), Formula (Ic) or preferred compounds of the invention, or salt, pro-drug or solvate thereof:

- (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- (b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and
- 25 (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and premenopausal breast cancer.

- 30 The compounds of Formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I).

- 18 -

Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- 10 d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable
15 pharmaceutically-acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters.

20 An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and related compounds which as a result of the in-vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy.
25 A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for
30 example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is

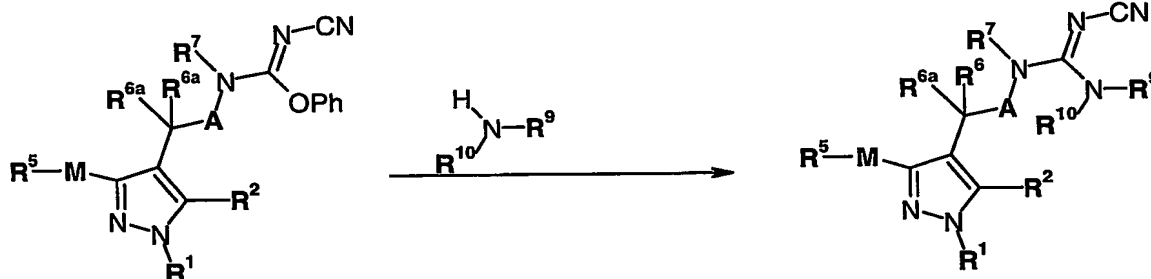
- 19 -

sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or

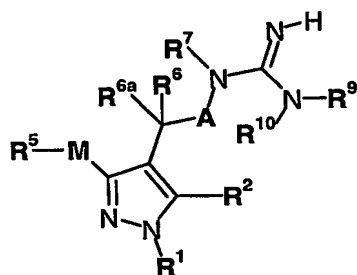
5 tris-(2-hydroxyethyl)amine.

The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (f) as follows, these processes are provided as a further feature of the invention:-

- (a) for compounds wherein **X** is N and **R**⁸ is CN, reaction of a compound of
10 formula **XXXII** as follows

**XXXII****XXXIII**

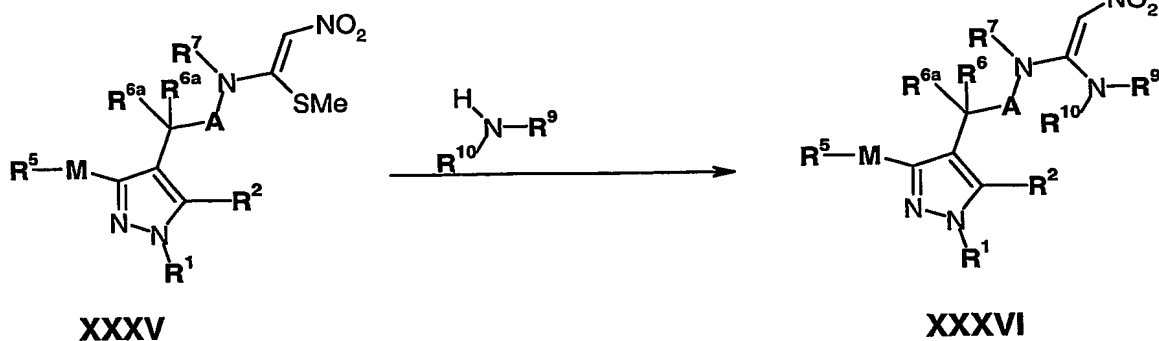
- (b) for compounds wherein **X** is N and **R**⁸ is hydrogen, cleavage of the cyano group of compound of formula **XXXIII** in the presence of acid to produce compound of formula **XXXIV**

**XXXIV**

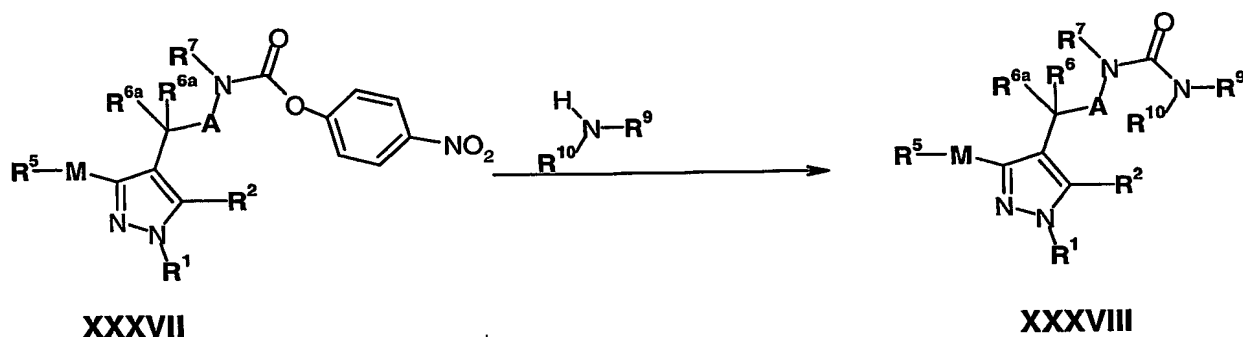
15

- (c) for compounds wherein **X** is CH and **R**⁸ is NO₂, reaction of compound of formula **XXXV** as follows

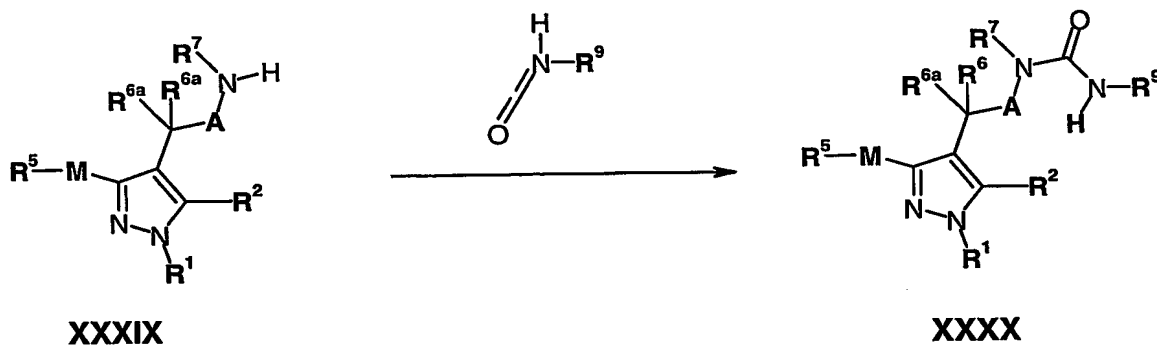
- 20 -



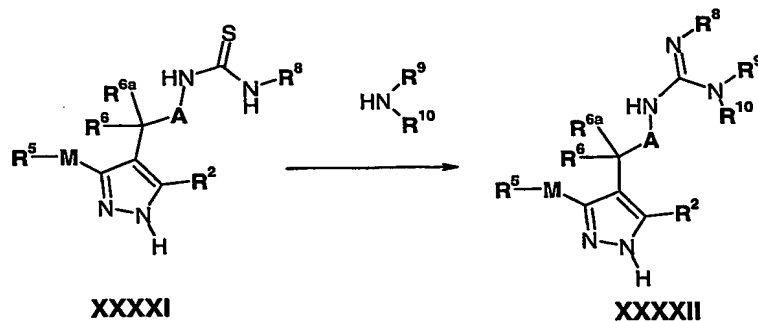
- (d) for compounds where $X-R^8$ is O, reaction of compound of formula XXXVII as follows



- 5 (e) for compounds where $X-R^8$ is O, reaction of compound of formula XXXIX as follows



- (f) to form a compound wherein X is nitrogen and Reaction of a compound of formula XXXXI as follows



- 21 -

and thereafter if necessary:

- i) converting a compound of the Formula (I) into another compound of the Formula (I);
- ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

5 It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the addition and subsequent removal of one or more protecting groups.

10 The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

 A suitable protecting group for an amino or alkylamino group is, for example, an acyl
15 group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl
20 group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for
25 example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

 A suitable protecting group for a hydroxy group is, for example, an acyl group, for
30 example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with

- 22 -

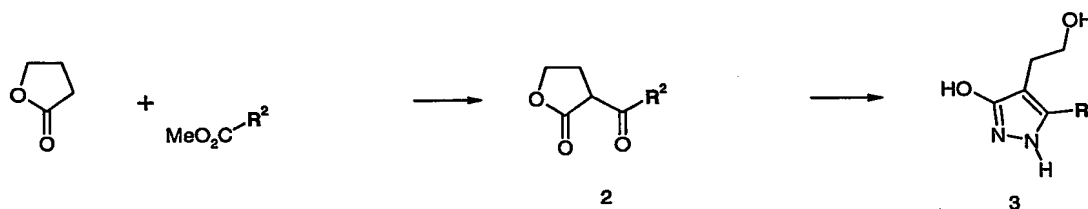
a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

10

EXPERIMENTAL

GENERAL REACTION SCHEMES



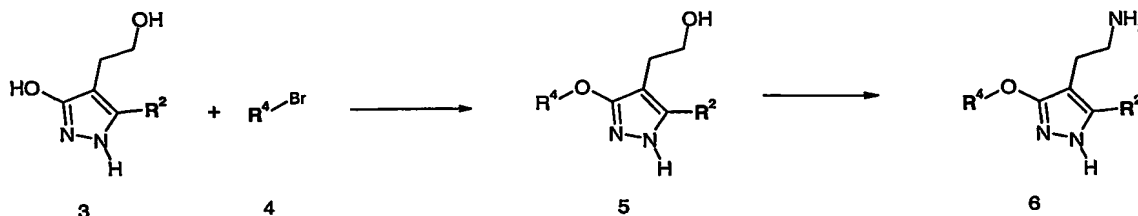
Scheme a

15 Pyrazoles, such as 3 can be synthesised in two steps (Scheme a):

(1) by the reaction of a lactone with the appropriate ester using a Claisen condensation to form a compound of formula 2, under conditions of an inert atmosphere, such as argon, at a temperature of about 0°C in a suitable solvent such as THF.

(2) followed by cyclization of a compound of formula 2 with hydrazine to form the pyrazole

20 3, at a room temperature in a suitable solvent such as ethanol.



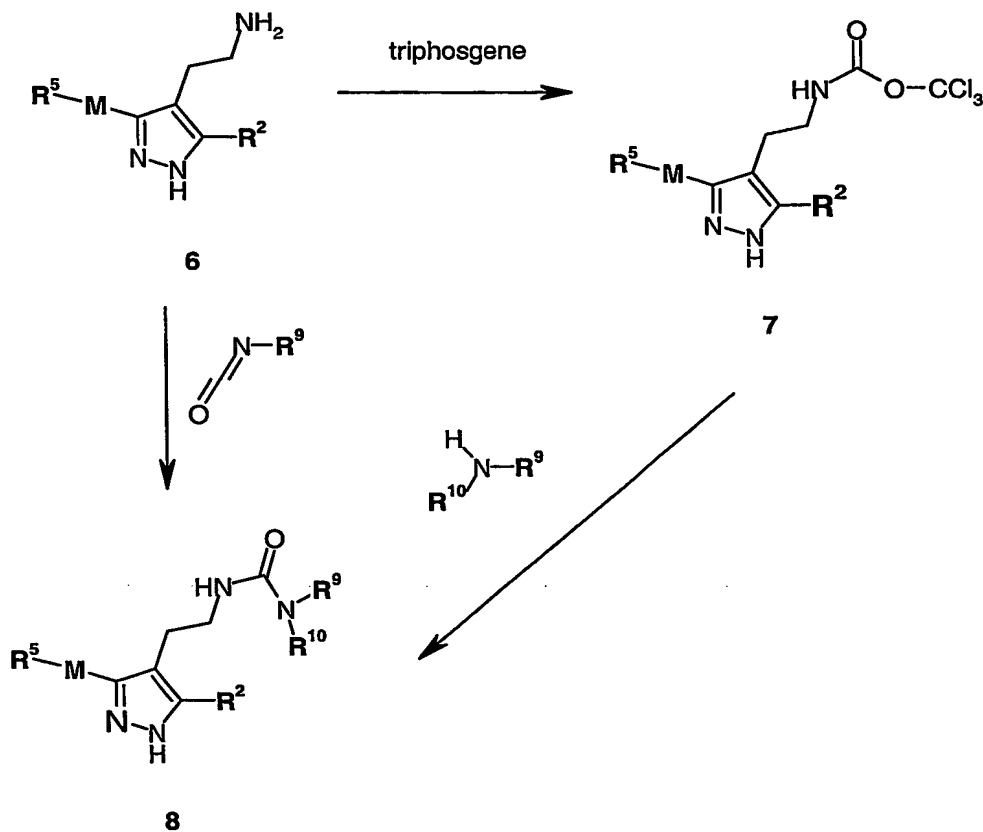
Scheme b

The pyrazole 3 can undergo a selective alkylation reaction with a compound of formula 4, under conditions of an inert atmosphere, such as argon, in the presence of a suitable base, such as potassium carbonate in a suitable solvent such as DMA at a temperature of about 90°C , to form a compound of formula 5. Then the amine 6 can be

25

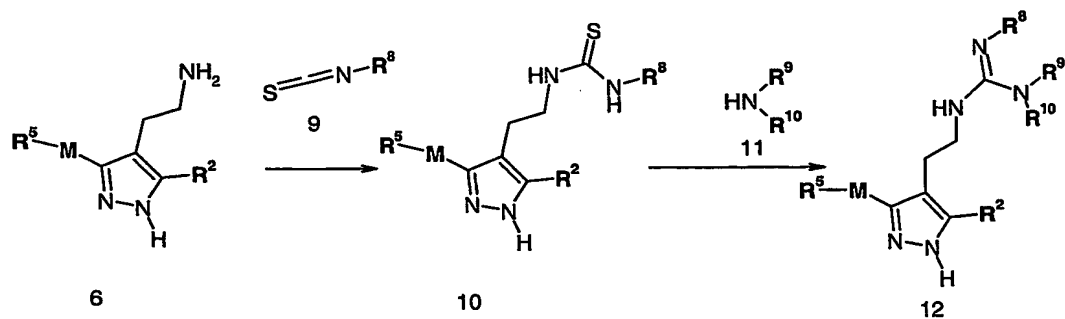
- 23 -

prepared from a compound of formula **5** and phthalimide using a Mitsunobu reaction with an activating agent such as diethyldiazocarbonate (DEAD), diisopropyldiazocarbonate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene, toluene, tetrahydrofuran or mixtures thereof, followed by deprotection with hydrazine (Scheme b).



Scheme c.

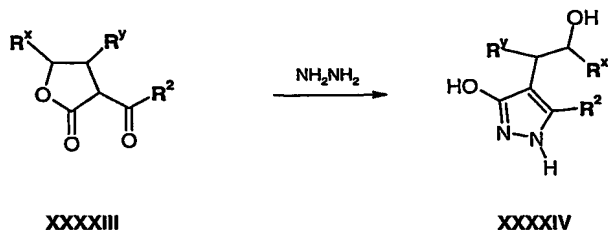
A suitable pyrazole **6** can be converted to a urea by either direct treatment with an isocyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**6**→**7**) followed by addition of an amine (**7**→**8**), bearing the required substitution to yield **8** (Scheme c).



- 24 -

A suitable pyrazole (6) can be converted to a guandine or guanidine derivative (12) by reaction with a suitable isothiocyanate (9) to form a compound of formula 10, followed by displacement by a suitable amine (11) (Scheme d).

Thus, according to a further feature of the invention there is provided a process for the
5 synthesis of a substituted pyrazole of formula XXXXIV which comprises reaction of a compound of formula XXXXIII with hydrazine.



wherein:

R^2 is as defined above; and

10 R^x and R^y are independently selected from: optionally substituted alkyl, optionally substituted aryl or optionally substituted heterocycl.

According to a further feature of the invention there is provided an intermediate compound of formula XXXXIII as defined above.

15 EXAMPLES

The invention will now be illustrated with the following non-limiting Examples in which, unless otherwise stated:

- (i) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids such as drying agents by
20 filtration;
- (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;
- (iii) yields are given for illustration only and are not necessarily the maximum attainable;
- 25 (iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

- 25 -

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

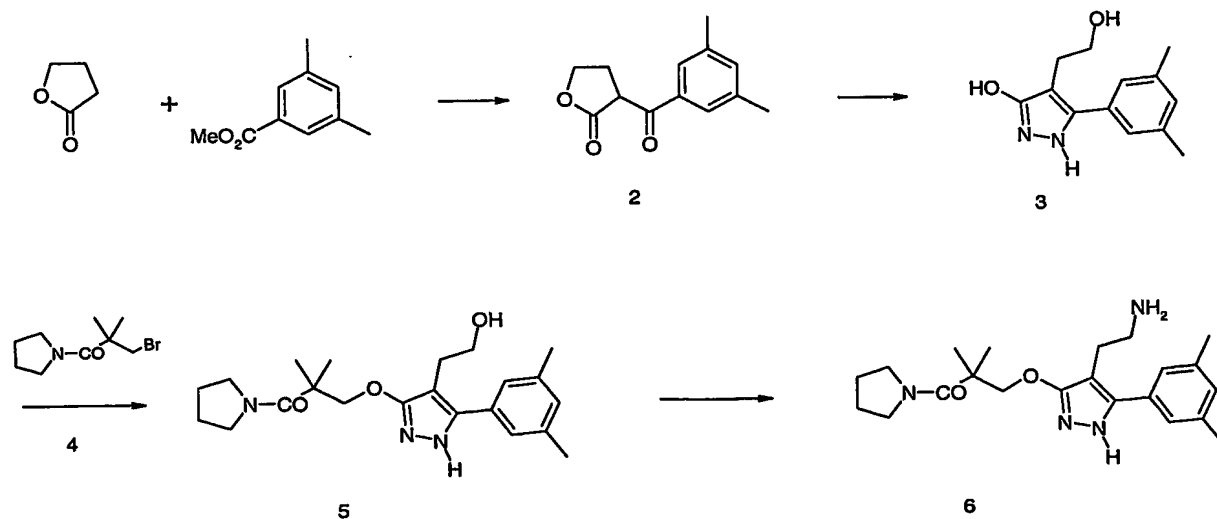
5

Abbreviations

DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethylazodicarboxylate
DMSO	dimethyl sulphoxide
10 DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DNS	2,4-dinitrobenzenesulphonyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	hydrochloride
15 HOBt	1-hydroxybenotriazole
LHMDS	lithium bis(trimethylsilyl)amide
THF	tetrahydrofuran

Starting Materials

20 The starting material were prepared as follows:-



A solution of methyl 3,5-dimethylbenzoate (25 g ; 152 mmol) and butyrolactone (40 ml ; 520 mmol) in THF (300 ml) under argon was cooled to 0°C and treated dropwise with LHMDS (200 ml ; 200 mmol ; 1M in hexanes). The mixture was stirred and allowed to warm to room

- 26 -

temperature overnight. The THF was evaporated. The residue was taken up in Et₂O and the organic phase was washed with sat. aq. NaHCO₃, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/hexanes (20 to 40% EtOAc) to give an oil which slowly crystallised to give **2** as a white solid (9.2 g). During the chromatography, the starting material methyl 3,5-dimethylbenzoate (12.4g) was recovered.

Yield : 55% based on recovered methyl 3,5-dimethylbenzoate.

¹H NMR spectrum (CDCl₃) : 2.39 (s, 6H) ; 2.5 (m, 1H) ; 2.82 (m, 1H) ; 4.41 (m, 1H) ; 4.51 (m, 2H) ; 7.25 (s, 1H) ; 7.65 (s, 2H).

MS-ESI : 219 [M+H]⁺

Compound **2** (7.43 g ; 34 mmol) was dissolved in EtOH (200 ml) and hydrazine hydrate (17.2 ml ; 354 mmol) was added. The mixture was stirred for 30 min. The solvent was evaporated and the residue was triturated with pentane to give **3** as a white solid (7.05 g).

Yield : 90%

¹H NMR spectrum (DMSO d₆) : 2.32 (s, 6H) ; 2.58 (t, 2H) ; 3.50 (t, 2H) ; 4.8 (br s, 1H) ; 7.01 (s, 1H) ; 7.14 (s, 2H) ; 9.5 (br s, 1H).

MS-ESI : 233 [M+H]⁺

A mixture of **3** (4.26 g ; 18.4 mmol) and **4** (4.51 g ; 19.3 mmol) in DMA (40 ml) under argon was treated with K₂CO₃ (5.07 g ; 36.7 mmol). The mixture was stirred and heated at 90°C for 2h. The mixture was poured into sat. aq. NaHCO₃, extracted with EtOAc and the organic phase was washed with water, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) to give the alcohol **5** as a pale yellow oil (6.56 g).

Yield : 93%

¹H NMR spectrum (DMSO d₆) : 1.30 (s, 6H) ; 1.8 (m, 4H) ; 2.33 (s, 6H) ; 2.55 (m, 2H) ; 3.32 (m, 2H) ; 3.5 (m, 4H) ; 4.17 (s, 2H) ; 4.62 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 386 [M+H]⁺

- 27 -

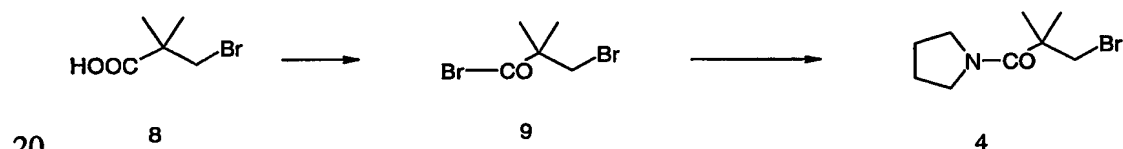
A mixture of **5** (3.85 g ; 10 mmol), phthalimide (1.62 g ; 11 mmol) and triphenylphosphine (10.5 g ; 40 mmol) in THF (100 ml) at 0°C under argon was treated with DEAD (6.33 ml ; 40 mmol). The mixture was stirred at this temperature for 1h when water was added. The mixture was extracted with Et₂O and the organic phase was washed with water, brine and dried over 5 MgSO₄.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (5 ml ; 100 mmol). The mixture was stirred for 1.5h and then the EtOH was partially evaporated. Addition of CH₂Cl₂ caused precipitation of phthalhydrazide which was filtered and rinsed with CH₂Cl₂. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) and then MeOH/CH₂Cl₂ (0 to 8% MeOH) to give **6** as a beige solid (2.34 g).

Yield : 61%

15 ¹H NMR spectrum (DMSO d₆) : 1.30 (s, 6H) ; 1.79 (m, 4H) ; 2.33 (s, 6H) ; 2.52 (m, 2H) ; 2.67 (t, 2H) ; 3.5 (m, 4H) ; 4.18 (s, 2H) ; 7.03 (s, 1H) ; 7.14 (s, 2H) ; 8.95 (br s, 1H).
MS-ESI : 385 [M+H]⁺

Starting material 4 was prepared as follows:-



A mixture of **8** (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up directly in CH₂Cl₂ (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH₂Cl₂ (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH₂Cl₂, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (5 to 10% EtOAc) to give **4** as a white solid (6.5 g).

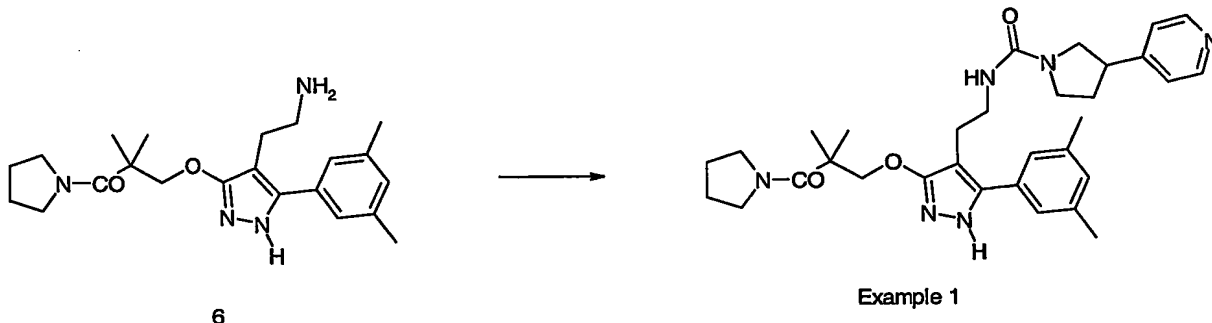
30

Yield : 70%

- 28 -

¹H NMR spectrum (DMSO d₆) : 1.39 (s, 6H) ; 1.9 (m, 4H) ; 3.57 (m, 4H) ; 3.62 (s, 2H)MS-ESI : 235 [M+H]⁺**Example 1**

- 5 **3-[2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propoxy]-4-[2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrazole**



A solution of **6** (150 mg ; 0.39 mmol) in CH₂Cl₂ (2 ml) was cooled to 0°C.

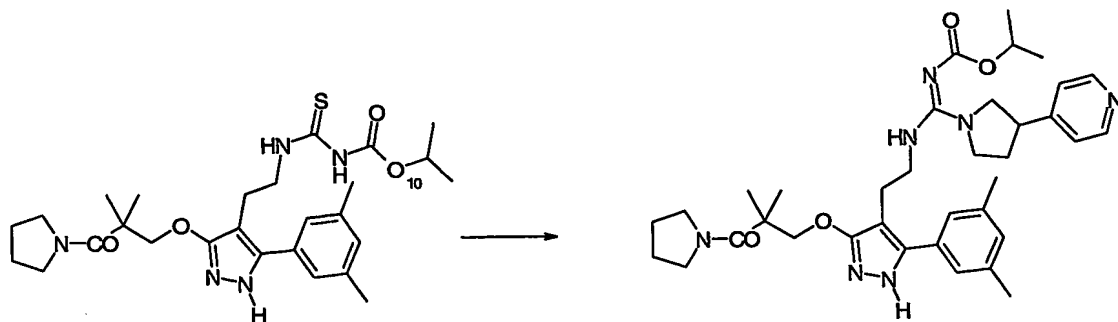
- 10 Diisopropylethylamine (136 ul ; 0.78 mmol) was added followed by a solution of 4-nitrophenyl chloroformate (83 mg ; 0.41 mmol) in CH₂Cl₂ (2 ml). The mixture was stirred for 3h when a solution of 4-(3-pyrrolidinyl)-pyridine (70 mg ; 0.47 mmol) in CH₂Cl₂ (2 ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was directly purified by flash chromatography eluting with increasingly polar mixtures of
- 15 MeOH/EtOAc (0 to 10% MeOH) to give **Example 1** as a beige solid (95 mg).

Yield : 44%

- ¹H NMR spectrum (DMSO d₆) : 1.29 (s, 6H) ; 1.75 (m, 4H) ; 1.95 (m, 1H) ; 2.2 (m, 1H) ; 2.31 (s, 6H) ; 2.56 (m, 2H) ; 3.1-3.4 (m, 6H) ; 3.5 (m, 4H) ; 3.64 (m, 1H) ; 4.18 (s, 2H) ; 6.22
- 20 (t, 1H) ; 6.99 (s, 1H) ; 7.21 (s, 2H) ; 7.27 (d, 2H) ; 8.48 (d, 2H).

MS-ESI : 559 [M+H]⁺

- 29 -

Example 2**3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-****4-[2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole****Example 2**

- 5 A solution of **10** (260 mg ; 0.5 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°C. EDCI (145 mg ; 0.75 mmol) and diisopropylethylamine (130 ul ; 0.75 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (111 mg ; 0.75 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH₂Cl₂ and the organic phase was
- 10 washed with sat. aq. NaHCO₃, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) to give **Example 2** as a beige solid (277 mg).

Yield : 86%

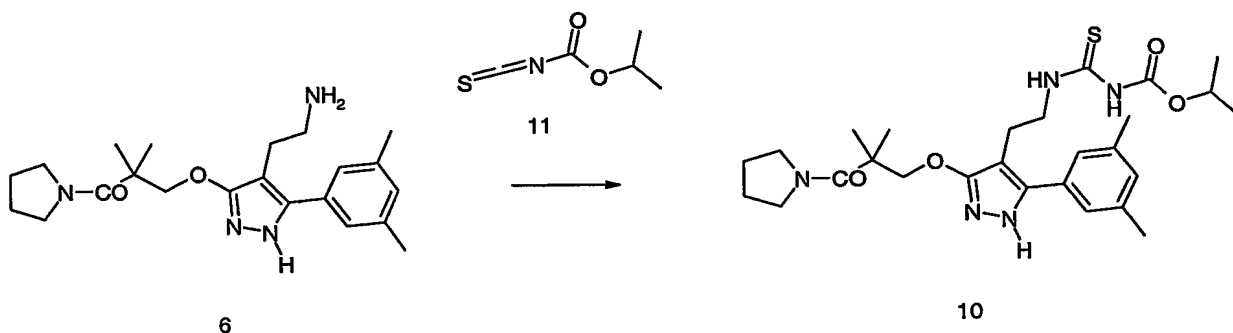
15

¹H NMR spectrum (DMSO d₆) : 1.07 (m, 6H) ; 1.29 (s, 6H) ; 1.8 (m, 4H) ; 1.95 (m, 1H) ; 2.2 (m, 1H) ; 2.30 (s, 6H) ; 2.65 (m, 2H) ; 3.2-3.4 (m, 6H) ; 3.5 (m, 4H) ; 3.65 (m, 1H) ; 4.18 (s, 2H) ; 4.6 (m, 1H) ; 6.95 (m, 1H) ; 7.00 (s, 1H) ; 7.12 (s, 2H) ; 7.27 (d, 2H) ; 8.49 (d, 2H).

20 MS-ESI : 644 [M+H]⁺

- 30 -

The starting material **10** was prepared as follows:-



- 5 A solution of **6** (200 mg ; 0.52 mmol) in CH₂Cl₂ (2 ml) was cooled to 0°C. A solution of **11** (115 mg ; 0.78 mmol) was added and the mixture was allowed to warm to room temperature for 1h. The mixture was treated with water, diluted with CH₂Cl₂ and the organic phase was washed with brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of Et₂O/hexanes (0 to 100% Et₂O) to give **10** as a
- 10 beige solid (260 mg).

Yield : 94%

¹H NMR spectrum (DMSO d₆) : 1.22 (m, 6H) ; 1.31 (s, 6H) ; 1.8 (m, 4H) ; 2.32 (s, 6H) ; 2.71 (m, 2H) ; 3.5 (m, 4H) ; 3.74 (m, 2H) ; 4.20 (s, 2H) ; 4.83 (m, 1H) ; 7.02 (s, 1H) ; 7.17 (s, 2H) ; 9.89 (t, 1H) ; 10.81 (s, 1H).

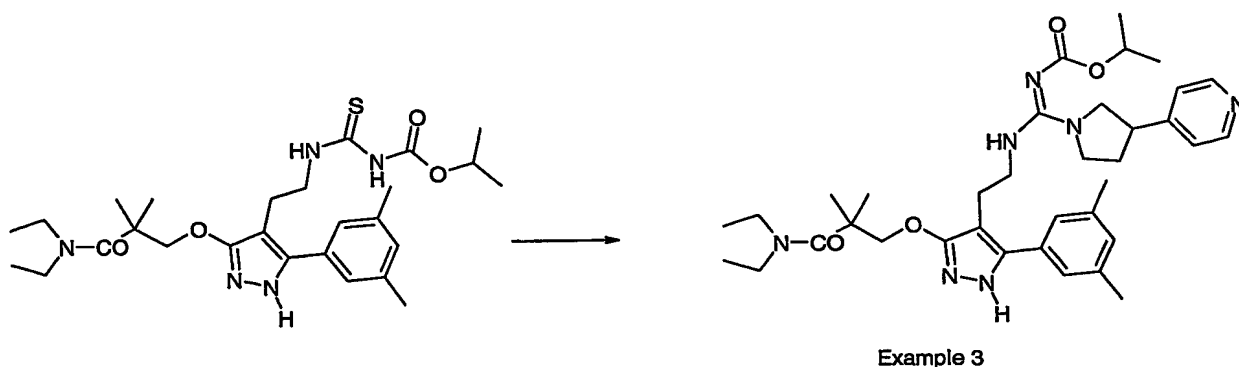
- 15 MS-ESI : 530 [M+H]⁺

Example 3

3-[2,2-dimethyl-3-oxo-3-(N,N-diethylamino)propyl]-

4-[2-(N'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-

- 20 dimethylphenyl)-1H-pyrazole



A solution of **Bb4** (156 mg ; 0.29 mmol) in CH₂Cl₂ (2 ml) was cooled to 0°C. EDCI (85 mg ;

- 31 -

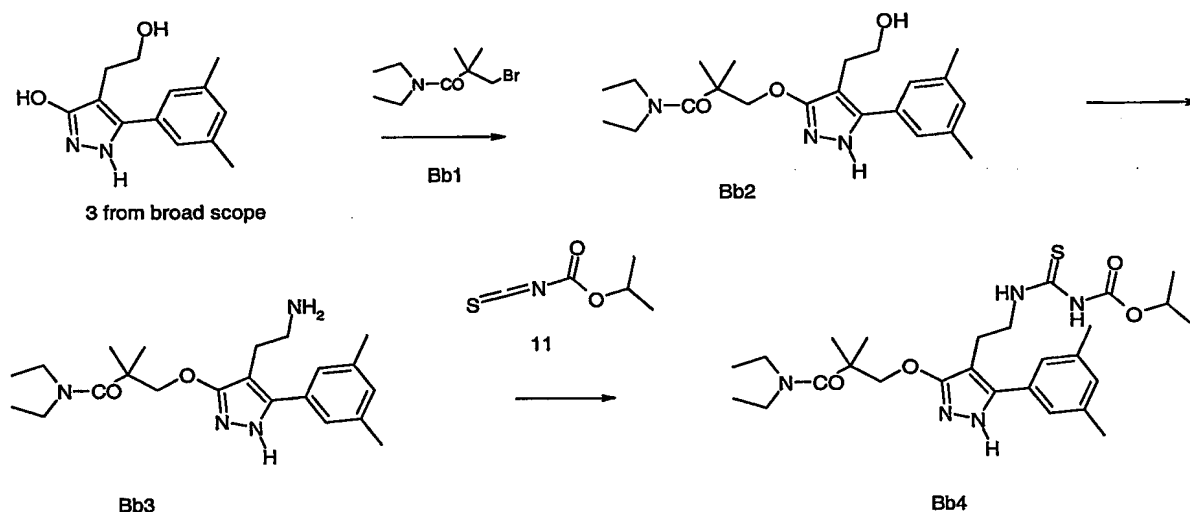
0.44 mmol) and diisopropylethylamine (77 μ l ; 0.44 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (56 mg ; 0.38 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH_2Cl_2 and the organic phase was washed with sat. aq. NaHCO_3 , brine and dried over MgSO_4 . The residue was purified by flash chromatography eluting with increasingly polar mixtures of $\text{MeOH}/\text{CH}_2\text{Cl}_2$ (0 to 100% MeOH) to give **Example 3** as a beige solid (180 mg).

Yield : 96%

^1H NMR spectrum ($\text{DMSO } d_6$) : 1.07 (m, 12H) ; 1.31 (s, 6H) ; 1.93 (m, 1H) ; 2.23 (m, 1H) ; 2.30 (s, 6H) ; 2.65 (m, 2H) ; 3.2-3.55 (m, 10H) ; 3.57 (m, 1H) ; 4.17 (s, 2H) ; 4.58 (m, 1H) ; 6.95 (m, 1H) ; 7.00 (s, 1H) ; 7.13 (s, 2H) ; 7.27 (d, 2H) ; 8.50 (d, 2H) ; 11.9 (br s, 1H).

MS-ESI : 646 $[\text{M}+\text{H}]^+$

The starting material **Bb4** was prepared as follows:-



15 A mixture of **3** (1.23 g ; 5.3 mmol) and **Bb1** (1.32 g ; 5.5 mmol) in DMA (20 ml) under argon was treated with K_2CO_3 (1.46 g ; 10.6 mmol). The mixture was stirred and heated at 70°C for 2h. The mixture was poured into sat. aq. NaHCO_3 , extracted with EtOAc and the organic phase was washed with water, brine and dried over MgSO_4 . The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/ CH_2Cl_2 (0 to 100% EtOAc) to give the alcohol **Bb2** as a pale yellow oil (1.92 g).

Yield : 94%

^1H NMR spectrum ($\text{DMSO } d_6$) : 1.08 (t, 6H) ; 1.32 (s, 6H) ; 2.33 (s, 6H) ; 2.57 (m, 2H) ; 3.38 (m, 4H) ; 3.5 (m, 1H) ; 4.18 (s, 2H) ; 4.61 (t, 1H) ; 7.04 (s, 1H) ; 7.16 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 388 $[\text{M}+\text{H}]^+$

- 32 -

A mixture of **Bb2** (1.92 g ; 4.96 mmol), phthalimide (0.8 g ; 5.46 mmol) and triphenylphosphine (5.24 g ; 20 mmol) in THF (50 ml) at 0°C under argon was treated with DEAD (3.2 ml ; 20 mmol). The mixture was stirred at this temperature for 2h when water was added. The mixture was extracted with Et₂O and the organic phase was washed with water, brine and dried over MgSO₄.

Evaporation gave a crude solid which, without further purification, was immediately taken up in EtOH (50 ml) and treated with hydrazine hydrate (2.5 ml ; 50 mmol). The mixture was stirred for 2h and then the EtOH was partially evaporated. Addition of CH₂Cl₂ caused precipitation of phthalhydrazide which was filtered and rinsed with CH₂Cl₂. The filtrate was evaporated and the residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) to give **Bb3** as a beige solid (0.865 g). Yield : 45%

¹H NMR spectrum (DMSO d₆) : 1.06 (t, 6H) ; 1.30 (s, 6H) ; 2.32 (s, 6H) ; 2.47 (m, 2H) ; 2.66 (t, 2H) ; 3.35 (m, 4H) ; 4.16 (s, 2H) ; 7.02 (s, 1H) ; 7.13 (s, 2H) ; 11.9 (br s, 1H).

MS-ESI : 387 [M+H]⁺

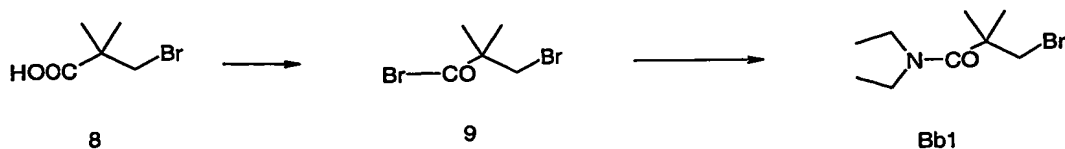
A solution of **Bb3** (210 mg ; 0.544 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°C. A solution of **11** (120 mg ; 0.82 mmol) was added and the mixture was allowed to warm to room temperature for 1h. The mixture was treated with water, diluted with CH₂Cl₂ and the organic phase was washed with brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with CH₂Cl₂ to give **Bb4** as a beige solid (235 mg).

Yield : 81%

¹H NMR spectrum (CDCl₃) : 1.18 (t, 6H) ; 1.27 (d, 6H) ; 1.44 (s, 6H) ; 2.38 (s, 6H) ; 2.87 (m, 2H) ; 3.45 (m, 4H) ; 3.88 (m, 2H) ; 4.36 (s, 2H) ; 4.93 (m, 1H) ; 7.04 (s, 1H) ; 7.11 (s, 2H) ; 7.81 (s, 1H) ; 8.9 (s br, 1H) ; 9.7 (s, 1H).

MS-ESI : 532 [M+H]⁺

Starting material **Bb1** was prepared as follows:-



- 33 -

A mixture of **8** (14.48 g ; 80 mmol) and oxalyl bromide (43.2 g ; 200 mmol) containing one drop of DMF was heated at 50°C for 2h and then cooled. The excess of oxalyl bromide was evaporated and the residue azeotroped with toluene to give crude **9** which was taken up directly in CH₂Cl₂ (25 ml) and cooled to 0°C. Diisopropylethylamine (14 ml ; 80 mmol) was added followed by a solution of pyrrolidine (3.3 ml ; 40 mmol) in CH₂Cl₂ (30 ml). The mixture was allowed to warm to room temperature overnight and was diluted with CH₂Cl₂, washed with aq. HCl (2N), aq. NaOH (1N), water, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (5 to 10% EtOAc) to give **Bb1** as a white solid (6.5 g).

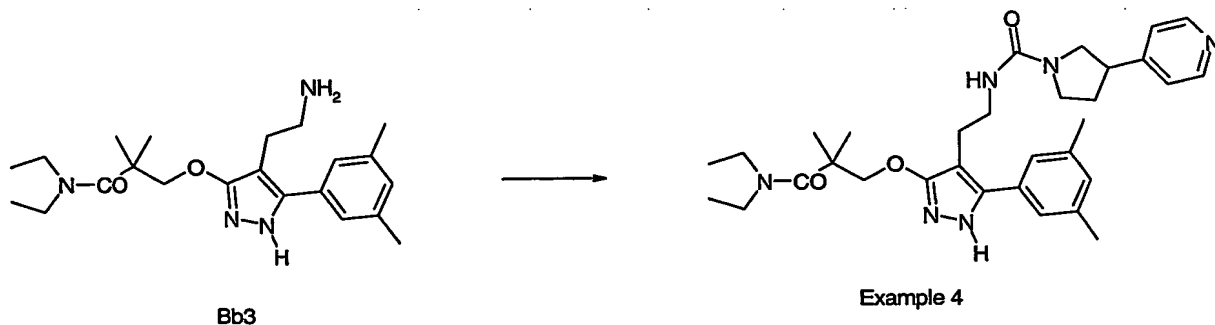
Yield : 70%

¹H NMR spectrum (DMSO d₆) : 1.19 (m, 6H) ; 1.42 (s, 6H) ; 3.41 (m, 4H) ; 3.65 (s, 2H)

MS-ESI : 237 [M+H]⁺

Example 4

3-[2,2-dimethyl-3-oxo-3-(N,N-diethylamino)propyl]-4-[2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrazole



A solution of **Bb3** (150 mg ; 0.39 mmol) in CH₂Cl₂ (2 ml) was cooled to 0°C.

Diisopropylethylamine (135 ul ; 0.78 mmol) was added followed by a solution of 4-nitrophenyl chloroformate (83 mg ; 0.41 mmol) in CH₂Cl₂ (2 ml). The mixture was stirred for 3h when a solution of 4-(3-pyrrolidyl)-pyridine (70 mg ; 0.47 mmol) in CH₂Cl₂ (2 ml) was added and the mixture was allowed to warm to room temperature overnight. The mixture was directly purified by flash chromatography eluting with increasingly polar mixtures of MeOH/EtOAc (0 to 10% MeOH) to give **Example 4** as a beige solid (138 mg).

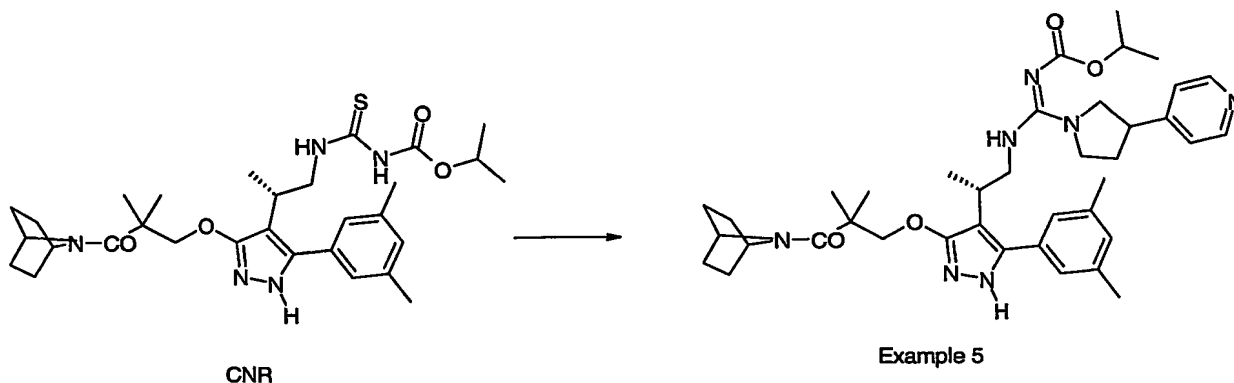
Yield : 63%

¹H NMR spectrum (DMSO d₆) : 1.05 ; (m, 6H) ; 1.32 (s, 6H) ; 1.89 (m, 1H) ; 2.2 (m, 1H) ; 2.31 (s, 6H) ; 2.57 (m, 2H) ; 3.1-3.4 (m, 10H) ; 3.64 (m, 1H) ; 4.17 (s, 2H) ; 6.22 (t, 1H) ; 6.99 (s, 1H) ; 7.22 (s, 2H) ; 7.27 (d, 2H) ; 8.48 (d, 2H) ; 11.9 (br s, 1H).

- 34 -

MS-ESI : 561 [M+H]⁺**Example 5****3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propyl]-**

5 **4-[1*S*-methyl-2-(*N*'-isopropoxycarbonyl-3-pyrid-4-yl-pyrrolidin-1-ylcarboximidamido)ethyl]-5-(3,5-dimethylphenyl)-1*H*-pyrazole**



A solution of **CNR** (141 mg ; 0.25 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°C. EDCI (72 mg ; 0.37 mmol) and diisopropylethylamine (65 ul ; 0.37 mmol) were added followed by 4-(3-pyrrolidyl)-pyridine (46 mg ; 0.31 mmol) and the mixture was allowed to warm to room temperature overnight. The mixture was diluted with CH₂Cl₂ and the organic phase was washed with sat. aq. NaHCO₃, brine and dried over MgSO₄. The residue was purified by flash chromatography eluting with increasingly polar mixtures of EtOAc/CH₂Cl₂ (0 to 100% EtOAc) to give **Example 5** as a beige solid (128 mg).

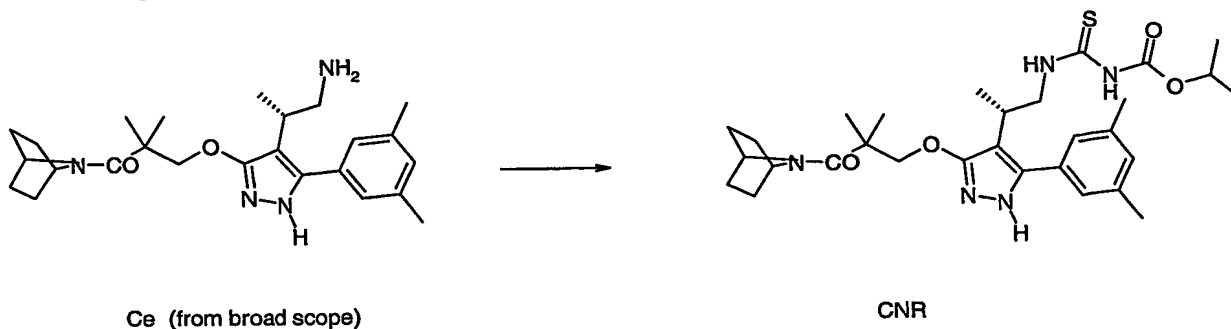
Yield : 78%

¹H NMR spectrum (DMSO d₆) : 1.05 (m, 6H) ; 1.12 (m, 3H) ; 1.28 (s, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.91 (m, 1H) ; 2.2 (m, 1H) ; 2.30 (s, 6H) ; 2.95 (m, 1H) ; 3.2-3.7 (m, 7H) ; 4.17 (s, 2H) ; 4.56 (m, 3H) ; 7.01 (s, 1H) ; 7.04 (s, 1H) ; 7.06 (s, 1H) ; 7.2 (s br, 1H) ; 7.27 (dd, 2H) ; 8.49 (dd, 2H) ; 11.79 (s, 1H).

MS-ESI : 684 [M+H]⁺

- 35 -

The starting material **CNR** was prepared as follows:-



A solution of **Ce** (150 mg ; 0.35 mmol) in CH_2Cl_2 (5 ml) was cooled to 0°C . A solution of **11** (77 mg ; 0.53 mmol) in CH_2Cl_2 (1 ml) was added and the mixture was allowed to warm to room temperature for 1 h. The mixture was treated with water, diluted with CH_2Cl_2 and the organic phase was washed with brine and dried over MgSO_4 . The residue was purified by flash chromatography eluting with $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ (0-20% EtOAc) to give **CNR** as a gum (141 mg).

Yield : 70%

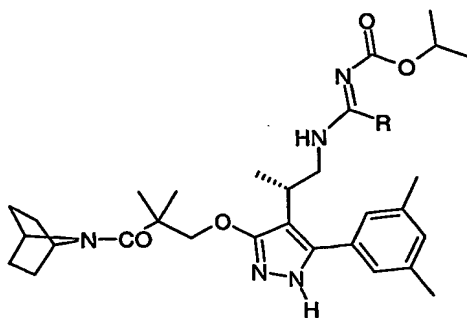
^1H NMR spectrum ($\text{DMSO}-d_6$) : 1.22 (d, 3H) ; 1.8 (m, 6H) ; 1.27 (m, 6H) ; 1.41 (m, 4H) ; 1.61 (m, 4H) ; 2.29 (s, 6H) ; 3.06 (q, 1H) ; 3.65 (m, 1H) ; 3.84 (m, 1H) ; 4.19 (m, 2H) ; 4.58 (s, 2H) ; 4.79 (m, 1H) ; 7.02 (s, 1H) ; 7.04 (s, 2H) ; 9.84 (s, 1H) ; 11.8 (s br, 1H).

MS-ESI : 570 $[\text{M}+\text{H}]^+$

15

Examples 5.1 – 5.2

The following examples were prepared in a similar manner to Example 5,

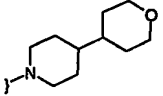


the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 5 given above:-

20

- 36 -

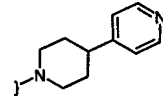
Example 5.1

R	CNR mg ; mmol	Amine mg ; mmol	EDCI mg ; mmol	DIEA μ l ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.3	68 ; 0.4	87; 0.45	80 ; 0.45	180 ; 85%	705 [M+H] ⁺

Chromato. – EtOAc/CH₂Cl₂ (0 to 100% EtOAc) and then MeOH/CH₂Cl₂ (0 to 5% MeOH)

¹H NMR spectrum (DMSO d₆) : 0.9-1.2 (m, 14H) ; 1.28 (m, 6H) ; 1.43 (m, 4H) ; 1.5 (m, 2H) ; 1.6 (m, 6H) ; 2.31 (s, 6H) ; 2.7 (m, 2H) ; 2.95 (m, 1H) ; 3.2-3.7 (m, 5H) ; 3.75 (m, 2H) ; 3.83 (m, 2H) ; 4.16 (s, 2H) ; 4.57 (m, 3H) ; 7.02 (s, 1H) ; 7.04 (s, 2H) ; 7.46 (s br, 1H) ; 11.80 (s, 1H).

Example 5.2

R	CNR mg ; mmol	Amine mg ; mmol	EDCI mg ; mmol	DIEA μ l ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.3	65 ; 0.4	87; 0.45	80 ; 0.45	172 ; 81%	698 [M+H] ⁺

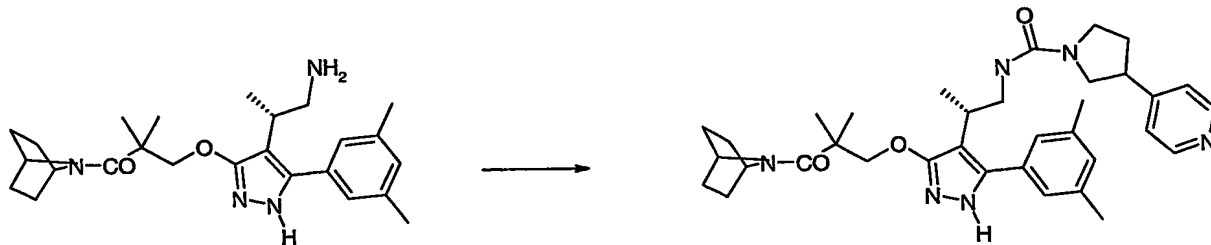
Chromato. – EtOAc/CH₂Cl₂ (0 to 100% EtOAc) and then MeOH/CH₂Cl₂ (0 to 5% MeOH)

10 ¹H NMR spectrum (DMSO d₆) : 1.07 (m, 6H) ; 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.5 (m, 2H) ; 1.62 (m, 4H) ; 1.72 (m, 2H) ; 2.30 (s, 6H) ; 2.7 (m, 1H) ; 2.9 (m, 2H) ; 2.95 (m, 1H) ; 3.2-3.4 (m, 2H) ; 3.85 (m, 2H) ; 4.17 (m, 2H) ; 4.57 (m, 3H) ; 7.01 (s, 1H) ; 7.06 (s, 2H) ; 7.18 (d, 2H) ; 7.5 (s br, 1H) ; 8.45 (d, 2H) ; 11.81 (s, 1H).

- 37 -

Example 6

3-[2,2-dimethyl-3-oxo-3-(azabicyclo[2.2.1]heptan-7-yl)propoxy]-4-[1S-methyl-2-(3-pyridin-4-ylpyrrolidin-1-carboxamido)ethyl]-5-(3,5-dimethylphenyl)-1H-pyrazole



Ce (from broad scope)

Example 6

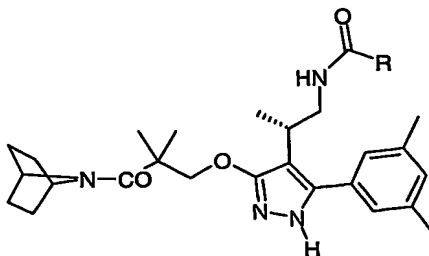
- 5 A solution of **Ce** (170 mg ; 0.4 mmol) in CH₂Cl₂ (5 ml) was cooled to 0°C and DIEA (140 μl ; 0.8 mmol) was added. A solution of 4-nitrophenyl chloroformate (85 mg ; 0.42 mmol) in CH₂Cl₂ (1 ml) was added and the mixture was allowed to stir for 30 min. 4-(3-Pyrrolidyl)-pyridine (71 mg ; 0.48 mmol) was added and the mixture allowed to warm to room temperature for 1 h. The mixture was directly purified by flash chromatography eluting with
- 10 MeOH/CH₂Cl₂ (0-10% MeOH) to give **Example 6** as a pale yellow powder (212 mg).

Yield : 88%.

- ¹H NMR spectrum (DMSO d₆) : 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ; 1.95 (m, 1H) ; 2.22 (m, 1H) ; 2.29 (s, 6H) ; 2.93 (m, 1H) ; 3.2-3.7 (m, 6H) ; 3.67 (m, 1H) ; 4.17 (s, 2H) ; 4.58 (s, 2H) ; 6.21 (m, 1H) ; 7.00 (s, 1H) ; 7.14 (s, 2H) ; 7.26 (m, 2H) ; 8.47 (m,
- 15 2H) ; 11.79 (s, 1H).

MS-ESI : 599 [M+H]⁺**Examples 6.1 – 6.**

The following examples were prepared in a similar manner to Example 6,

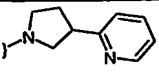


20

the table shows the **R** group relating to the above structure, the reaction conditions and characteristics for each example, corresponding to the description of the preparation of Example 6 given above:-

- 38 -

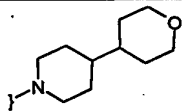
Example 6.1

R	Ce mg ; mmol	DIEA μ l ; mmol	4-NPC mg ; mmol	Amine mg ; mmol	Mass mg ; Yield	MS-ESI
	170 ; 0.4	140 ; 0.8	90 ; 0.42	71 ; 0.48	226 ; 94%	599 [M+H] ⁺

Chromato. –MeOH/ EtOAc (0 to 5% MeOH)

¹H NMR spectrum (DMSO d₆) : 1.11 (m, 3H) ; 1.28 (m, 6H) ; 1.42 (m, 4H) ; 1.62 (m, 4H) ;
 1.99 (m, 1H) ; 2.20 (m, 1H) ; 2.29 (s, 6H) ; 2.93 (m, 1H) ; 3.2-3.5 (m, 6H) ; 3.68 (m, 1H) ;
 5 4.17 (s, 2H) ; 4.58 (s, 2H) ; 6.15 (m, 1H) ; 7.00 (s, 1H) ; 7.14 (m, 2H) ; 7.24 (m, 1H) ; 7.29
 (m, 1H) ; 7.72 (m, 1H) ; 8.49 (m, 1H) ; 11.74 (s, 1H).

Example 6.2

R	Ce mg ; mmol	DIEA μ l ; mmol	4-NPC mg ; mmol	Amine mg ; mmol	Mass mg ; Yield	MS-ESI
	110 ; 0.26	90 ; 0.52	55 ; 0.27	52 ; 0.28	131 ; 81%	620 [M+H] ⁺

Chromato. – EtOAc/CH₂Cl₂ (0 to 100% EtOAc)

10 ¹H NMR spectrum (DMSO d₆) : 0.9 (m, 2H) ; 1.07 (m, 3H) ; 1.14 (m, 4H) ; 1.28 (m, 6H) ;
 1.4-1.7 (m, 12H) ; 2.30 (s, 6H) ; 2.9 (m, 1H) ; 3.2-3.4 (m, 6H) ; 3.82 (m, 2H) ; 3.96 (m, 2H) ;
 4.17 (m, 2H) ; 4.58 (m, 2H) ; 6.45 (m, 1H) ; 6.99 (s, 1H) ; 7.14 (s, 2H) ; 11.81 (s, 1H).

THERAPEUTIC USES

15 Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg,
 20 lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and
 25 ethylene glycol.

- 39 -

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of 0.1mgkg⁻¹ to 30mgkg⁻¹ (preferably, 5mgkg⁻¹ to 20mgkg⁻¹) of the compound, the compound
5 being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation
10 is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl β cyclodextrin may
15 be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according
20 to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis,
25 polycystic ovarian disease, uterine fibroids, prostatauxe, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

30 If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

- 40 -

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

- i) anti-angiogenic agents (for example linomide, inhibitors of integrin $\alpha v \beta 3$ function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated herein by reference);
- ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), inhibitors of testosterone 5α -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);
- iii) biological response modifiers (for example interferon);
- iv) antibodies (for example edrecolomab); and
- v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or

radiotherapy.

ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH
5 can be determined using the following in vitro assays.

Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer
(pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-
10 ethyl amide-GnRH, and the test compound. Incubation is at 4°C for 90 minutes to 2
hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC₅₀ of the test compound can be determined as the concentration of
15 the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

Compounds according to the present invention have activity at a concentration from 1nM to 5
µM.

Binding Assay Using Human GnRH Receptor

20 Crude membranes prepared from CHO cells expressing human GnRH receptors are
sources for the GnRH receptor. The binding activity of compounds according to the invention
can be determined as an IC₅₀ which is the compound concentration required to inhibit the
specific binding of [¹²⁵I]buserelin to GnRH receptors by 50%. [¹²⁵I]Buserelin (a peptide
GnRH analogue) is used here as a radiolabelled ligand of the receptor.

25

Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as
demonstrated by a reduction in GnRH-induced LH release.

30 Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar
male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a

- 42 -

12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS).

The glands are further processed by:-

- 5 1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2%
10 hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
- 15 7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the
20 collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of 3×10^5 cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being maintained in a humidified 5% CO₂/95% air atmosphere at 37°C for 3 to 4 days

25 Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

- 1.5 hours prior to the assay, the cells are washed three times with DMEM containing 0.37% NaHCO₃, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids
30 (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

- 43 -

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

5 Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have
10 activity at a concentration from 1nM to 5 µM.